Health Consultation

SUNNYSIDE AREA GROUNDWATER CONTAMINATION

Evaluation of Antibiotic, Steroid Hormone & Nitrate Compounds in Groundwater Near a Confined Animal Feeding Operation (CAFO)

WEISER, WASHINGTON COUNTY, IDAHO

MARCH 19, 2007

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Agency for Toxic Substances and Disease Registry
Division of Health Assessment and Consultation
Atlanta, Georgia 30333

Health Consultation: A Note of Explanation

An ATSDR health consultation is a verbal or written response from ATSDR to a specific request for information about health risks related to a specific site, a chemical release, or the presence of hazardous material. In order to prevent or mitigate exposures, a consultation may lead to specific actions, such as restricting use of or replacing water supplies; intensifying environmental sampling; restricting site access; or removing the contaminated material.

In addition, consultations may recommend additional public health actions, such as conducting health surveillance activities to evaluate exposure or trends in adverse health outcomes; conducting biological indicators of exposure studies to assess exposure; and providing health education for health care providers and community members. This concludes the health consultation process for this site, unless additional information is obtained by ATSDR which, in the Agency's opinion, indicates a need to revise or append the conclusions previously issued.

You May Contact ATSDR Toll Free at
1-800-CDC-INFO
or
Visit our Home Page at: http://www.atsdr.cdc.gov

HEALTH CONSULTATION

SUNNYSIDE AREA GROUNDWATER CONTAMINATION

Evaluation of Antibiotic, Steroid Hormone & Nitrate Compounds in Groundwater Near a Confined Animal Feeding Operation (CAFO)

WEISER, WASHINGTON COUNTY, IDAHO

Prepared By:

Idaho Department of Health and Welfare
Division of Health
Under a Cooperative Agreement with the
U.S. Department of Health and Human Services
Agency for Toxic Substances and Disease Registry

Foreword

The State of Idaho, Idaho Division of Health (IDOH), Bureau of Community and Environmental Health (BCEH) jointly prepared this public health consultation with the Agency for Toxic Substances and Disease Registry (ATSDR). ATSDR is part of the U.S. Department of Health and Human Services and is the principal federal public health agency responsible for health issues related to environmental contaminants. This health consultation was prepared in accordance with methodologies and guidelines developed by ATSDR.

The health consultation is an approach used by ATSDR and IDOH to respond to requests from concerned residents for health information on hazardous substances in the environment. The health consultation process evaluates sampling data collected from a hazardous waste site, determines whether exposures have occurred or could occur, reports any potential harmful effects, and recommends actions to protect public health.

Summary

What is the purpose of this health consultation?
Many of the wells in the area of the Sunnyside concentrated animal feeding operation (CAFO) have tested positive for nitrates, veterinary antibiotics, and the veterinary growth hormone 17-beta estradiol. The Sunnyside CAFO is believed to be the source of the antibiotics and 17-beta estradiol, and, to some extent, the source of the nitrates in these wells. The BCEH was requested to evaluate the potential health effects associated with exposure to groundwater from domestic wells in the Sunnyside area.

What pollutants were found in wells near the Sunnyside CAFO?
Nitrates, veterinary antibiotics, and the veterinary growth hormone 17-beta estradiol were detected in many wells in the area. It was determined that nitrates at levels above 10 mg/L pose a public health hazard, and that 17-beta estradiol poses a potential, though uncertain health hazard.

Who is most at risk?
For nitrates, infants are at greatest risk. For 17-beta estradiol, it is believed that children before and up to the end of puberty are potentially at greatest risk.

How can nitrates affect my child's health?
Nitrates are converted to nitrite in the body and can block the uptake of oxygen into the bloodstream. This often results in digestive and respiratory system problems. In severe cases, the condition can essentially cause the infant to suffocate.

How can 17-beta estradiol affect my child's health?
17-beta estradiol is known to cause excessively rapid growth in pre-pubertal children. The exact amount of 17-beta estradiol needed to cause this effect varies based on how much total estradiol the child's body is naturally producing at a given stage of development. It is also possible that 17-beta estradiol may cause early sexual development in girls and delayed sexual development in boys based on animal studies, though there are no human studies to support this conclusion.

How might we be exposed to nitrates and 17-beta estradiol?
Consuming water from a contaminated well (either via drinking the water or using it to prepare food) may expose a child to either nitrate or 17-beta estradiol at a sufficient dose to cause an effect.

Could exposure to either or both of these chemicals cause permanent health effects?
For nitrates, effects occur rapidly following an exposure and are not permanent provided the infant remains conscious. Lack of oxygen in the blood, indicated by loss of consciousness, can cause permanent brain damage. For 17-beta estradiol, rapid growth and development will not necessarily cause lasting health effects, but may potentially lead to chronic bone and joint pain. For both nitrates and 17-beta estradiol, effects will cease once exposure is no longer occurring. There is no long-term residue left over in the body.

What are the major recommendations of this health consultation?
The following recommendations should be considered:

1. No one should consume water from wells next to or down gradient of the CAFO due to the know hazard of nitrate contamination and the uncertainty about the safety of 17-beta estradiol concentrations found in these wells.

2. It is suggested that other wells down gradient (west, south, southwest) of the CAFO be tested for nitrates and 17-beta estradiol. If a well tests over 10 mg/L nitrates or tests positive for 17-beta estradiol, residents should cease consuming this water.

3. The Onion Dump (SE of the CAFO) should be inspected for potential remaining source(s) of 17-beta estradiol.

What is the public health action plan?
1. ATSDR and BCEH will provide the findings of this health consultation to the public.

2. BCEH will work with the Environmental Protection Agency (EPA) and Idaho Department of Environmental Quality (IDEQ) to have any remaining ponds or lagoons on the CAFO site drained and the water disposed of properly off-site.

3. BCEH will work with Idaho State Department of Agriculture (ISDA) and IDEQ to have the Onion Dump (SE of the CAFO) inspected for potential remaining source(s) of 17-beta estradiol if future well monitoring shows continued levels above the detection limit.

4. BCEH will work with Southwest District Health to provide clear notification to residents in the entire Sunnyside area. The message is that infants, particularly those less than 9 months old, should not be allowed to drink well water from this area, and infant formula or other foods should not be prepared for infants using well water from this area.

5. BCEH will work with Southwest District Health to ensure an alternative source of drinking water is available to residents whose wells are affected. BCEH will assist IDEQ state and local offices in their implementation of the Idaho Groundwater Quality Plan (IDEQ 1996).

Where do I get more information?
If you have questions or comments, please contact Dr. Kai Elgethun, BCEH, at 334-5682 or elgethun@dhw.idaho.gov.

Purpose and Statement of Issues

The Idaho State Department of Agriculture (ISDA) has requested that the Agency for Toxic Substances and Disease Registry (ATSDR) evaluate the potential for adverse health impacts and address specific community concerns related to concentrations of nitrates, hormones, and antibiotics found in groundwater wells in the Sunnyside area near Weiser, Idaho (Figure 1). ATSDR has jointly prepared this health consultation within the cooperative agreement program in the Bureau of Community and Environmental Health (BCEH), Idaho Division of Health (IDOH). The initial health risk consultation for the Sunnyside site was conducted by Dr. Jeffrey Fromm, Toxicologist for Idaho Department of Environmental Quality (IDEQ). Dr. Fromm's work is incorporated into the risk analysis presented here.

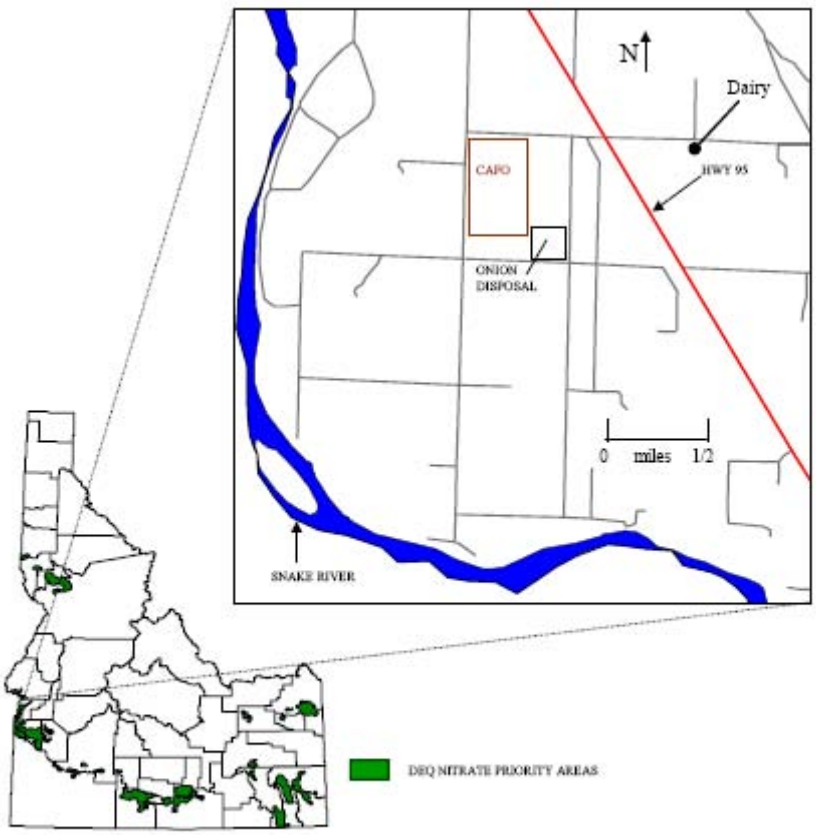


Figure 1. Sunnyside project area and location of DEQ nitrate priority areas
Source: ISDA / IDEQ

Background

As a result of citizen concern of possible groundwater contamination in the area surrounding a confined animal feeding operation (CAFO) and onion disposal site, the ISDA began to monitor groundwater in November 2002. Initial testing indicated that a majority of wells tested had elevated levels of nitrates.

Follow-up testing in April 2003 confirmed these results and isotope testing indicated an animal or human waste source of nitrates. Since large livestock CAFOs commonly use pharmaceuticals in their operations, ISDA analyzed one wastewater lagoon and one groundwater well sample for pharmaceuticals. Sulfamethazine and sulfadimethoxane (two antibiotics commonly used in CAFOs) were found in both samples, suggesting that the CAFO was impacting area groundwater. Subsequently, ISDA and IDEQ have monitored groundwater in 12 monitoring wells and 24 domestic wells biannually in the spring and fall for the past 3 years. The samples were tested for various analytes including: common ions, dissolved metals, bacteria, antibiotics, steroid hormones, and pesticides. The following report is based on data taken from summaries in the June 2006 ISDA/IDEQ report: "Assessment of Water Quality in the Sunnyside Area, Washington County, Idaho: 2006 Update", and from 2004 and 2005 laboratory reports.

Site Description

The extent of the land area being considered for health risk due to contamination is approximately one by three miles (inset map, Figure 1). The land is a mix of agricultural, commercial/light industrial, and residential usage. Specific uses include irrigated fields, a dairy, an onion disposal site, various businesses, and rural housing in addition to the CAFO. In addition to on-site storage, manure from the CAFO and dairy has been spread on local agricultural fields as fertilizer. Shallow (20 feet or less) groundwater conditions exist in this area. The sand and gravel soil conditions that exist in this area are conducive to leaching of contaminants. These hydrogeological characteristics predispose this site to an unusually high potential for groundwater contamination.

Sources of Contamination

Potential sources for leaching of nitrate, antibiotics, steroid hormones, and pesticides to groundwater include cattle manure, crop application of manure, wastewater lagoons associated with the CAFO or nearby dairy, crop application of nitrogen-based fertilizers, presence of legume crops, domestic and agricultural septic systems, and natural degradation of soils. Another potential source of antibiotic and steroid hormone leaching to groundwater could be the dumping of excess or expired animal medications, or leakage of these compounds from storage facilities. A potential source of pesticide leaching to groundwater could be direct application to crops.

Sampling

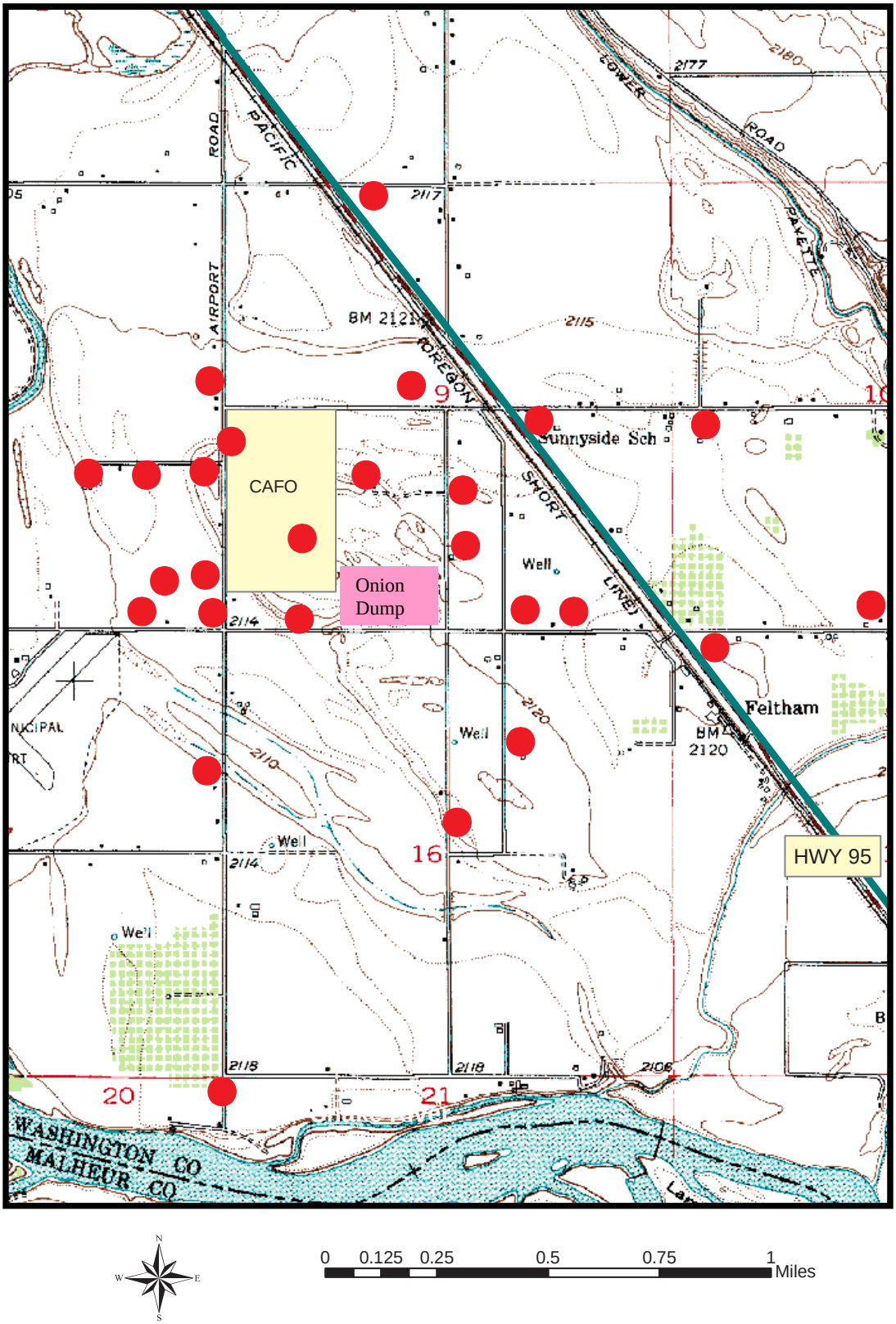
Twenty-two domestic wells within the CAFO and surrounding the CAFO were sampled beginning in November 2002 (Figure 2). In addition, 12 monitoring wells were drilled in 2004 and sampled from 2004 to present (Figure 3). Sampling was conducted by ISDA, IDEQ and the U.S Environmental Protection Agency (EPA). Nutrients, antibiotics, and steroid hormones were the focus of groundwater testing. All sample collection followed the established quality assurance project plan for preservation, handling, storage, and shipping. Field quality assurance/quality control protocols consisted of duplicate samples (at 10% of the sample load) along with blank samples (one set per sampling event). Field blanks consisted of laboratory grade deionized water. The blank samples were used to determine the integrity of the field team's sample handling, the cleanliness of the sample containers, and the accuracy of the laboratory methods.

Analyses

Samples were sent to the EPA-certified University of Idaho Analytical Sciences Laboratory (UIASL) in Moscow, Idaho. UIASL conducted tests for orthophosphorus, chloride, sulfate, bromide, and fluoride using EPA Method 300.0 (ion chromatography) and for nitrate, nitrite, and ammonia using EPA Method 350.1 (colorimetry). UIASL also conducted tests for antibiotics and steroid hormones using liquid chromatography/mass spectrometry, and pesticides using gas chromatography. Internal laboratory spikes and duplicates were also completed as part of UIASL's quality assurance program. In 2005, stable isotope analyses were conducted, using mass spectrometry, to determine the source of nitrates. Those samples were collected, frozen, and shipped to the Stable Isotope Laboratory, University of Idaho, Department of Forest Resources for analysis.

EPA Drinking Water Standards

The EPA is responsible for setting drinking water standards, called Maximum Contaminant Levels (MCLs). The MCL is the highest level of a chemical that is permitted in public drinking water systems. MCLs are set as close to maximum contaminant level goals (MCLGs) as feasible using the best available treatment technology and taking cost into consideration. MCLGs are the level of a contaminant in drinking water below which there is no known or expected risk to health. MCLGs allow for a margin of safety and are non-enforceable public health goals while MCLs are enforceable standards (EPA, February 2006; EPA, November 2006). Of the contaminants found in drinking water near the CAFO, only the nitrates and pesticides have existing MCLs. Currently there are no MCLs for steroid hormones or antibiotics (EPA, February 2006).



0 0.125 0.25 0.5 0.75 1 Miles

Figure 2: Sampled existing well locations (represented by large dots).

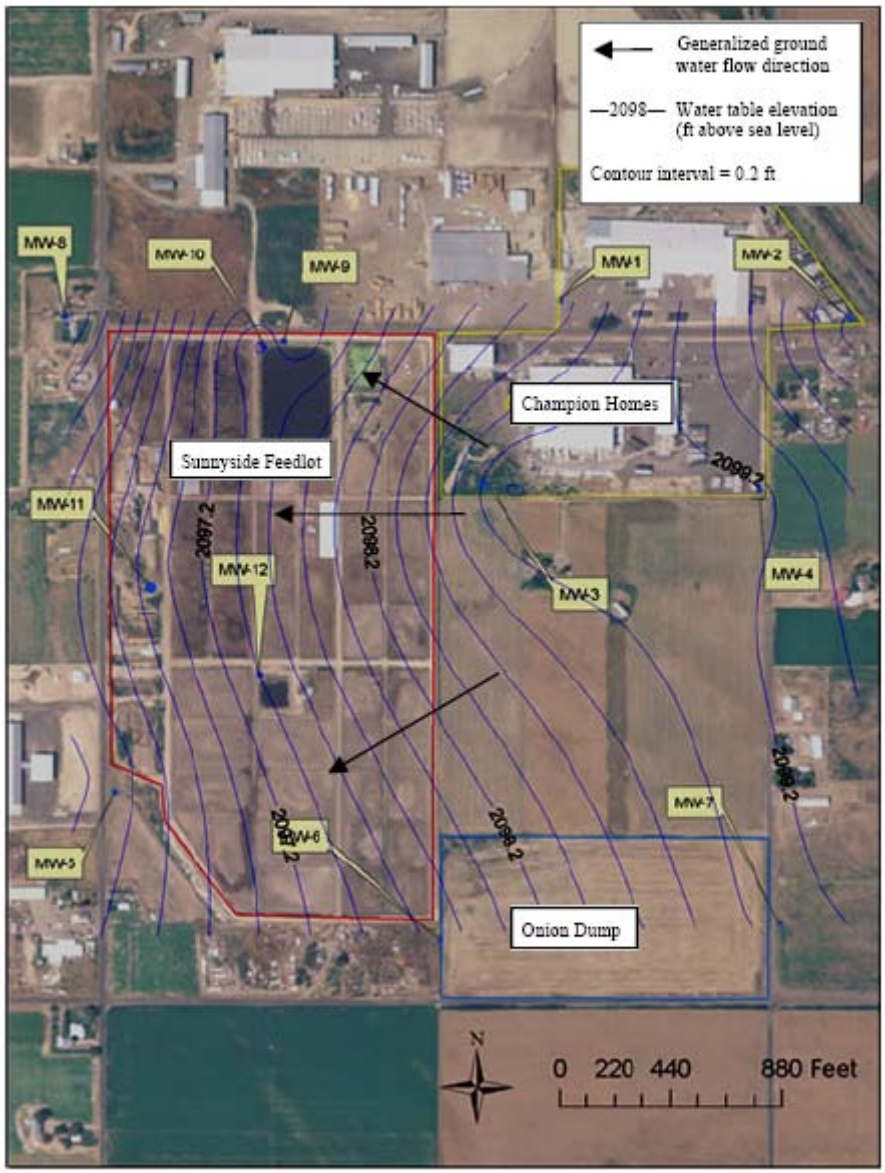


Figure 3: Monitoring well locations (new wells drilled for sampling) and direction of upper groundwater flow.
Source: ISDA / IDEQ

Results

Nitrates

The results of nitrate sampling from 2005 are shown in Figure 4 and Table 1. The results of nitrate sampling from 2006 are shown in Figure 5 and Table 2. A comparison of nitrate

groundwater concentration between the years 2002 and 2005 is shown in Figure 6. Over the testing years, some wells showed increased contaminant concentrations, while the contaminants in others decreased. Mean and median nitrate concentration for all wells did not change appreciably between years. Some wells increased between years, while others decreased. In addition to the EPA MCL, nitrate levels were also compared to the EPA Reference Dose (RfD), since technically the MCL is not a regulatory standard for private wells. These analyses are shown in the Discussion section. The wells most consistently above the MCL and RfD for nitrates were located in, immediately adjacent to or down gradient from the CAFO. Down gradient direction is shown in Figure 3 (direction of arrow), and is generally to the west-southwest of the CAFO.

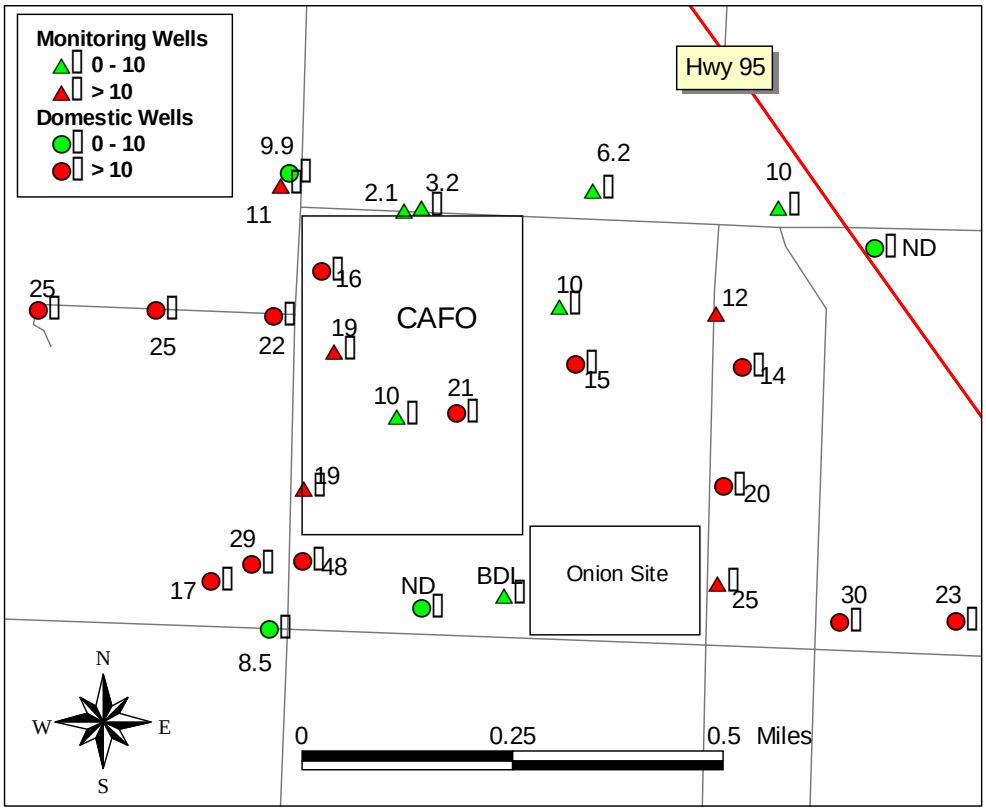


Figure 4: Nitrate concentrations (mg/L) in 17 domestic supply and 12 monitoring wells, November 2005. ND = non detect; BDL = below detection limit.

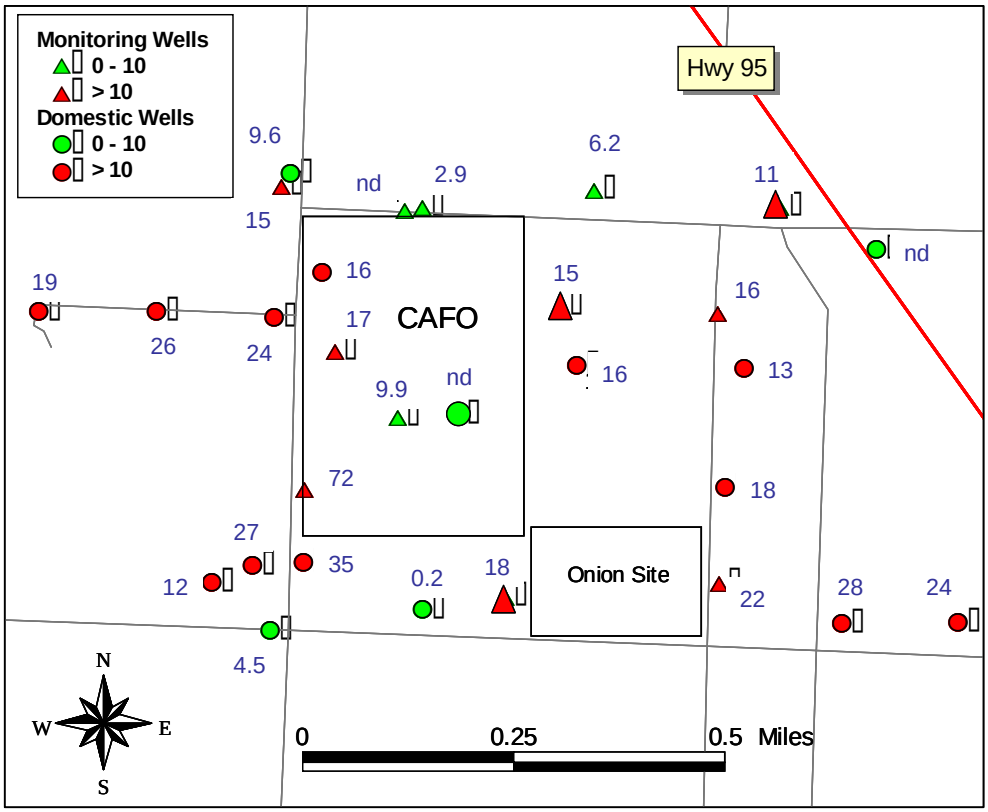


Figure 5: Nitrate concentrations (mg/L) in 17 domestic and 12 monitoring wells, May 2006. Oversized icons indicate values that changed between 2005 and 2006, from above the MCL to below the MCL, or vice versa. nd = non detect. EPA data from 2006 are estimated using a higher limit of detection and are not included here. See Table 2 for 2006 individual agency results.

Table 1: Nitrate concentration distribution and statistics in 36 wells, Fall 2005.

Concentration Statistics (mg/L)	Number of wells (% wells)
0.0 to 10.0	**15 (42%)**
>10.0	**21 (58%)**
Total	**36 (100%)**
Mean – 15 mg/L	
Median – 14 mg/L	
Maximum – 48 mg/L	

Table 2: Nitrate concentration distribution and statistics in 36 wells, May 2006.

Concentration Statistics (mg/l)	ISDA Number of wells (% wells)	IDEQ Number of wells (% wells)	EPA Number of wells (% wells)
0.0 to 10.0	**8 (35%)**	**4 (33%)**	**3 (27%)**
>10.0	**15 (65%)**	**8 (67%)**	**8 (73%)**
Total	**23 (100%)**	**12 (100%)**	**11 (100%)**
	Mean – 15 mg/L	**Mean—19 mg/L**	**Mean—14 mg/L**
	Median – 14 mg/L	**Median—15 mg/L**	**Median—15 mg/L**
	Maximum – 35 mg/L	**Maximum—72 mg/L**	**Maximum—35 mg/L**

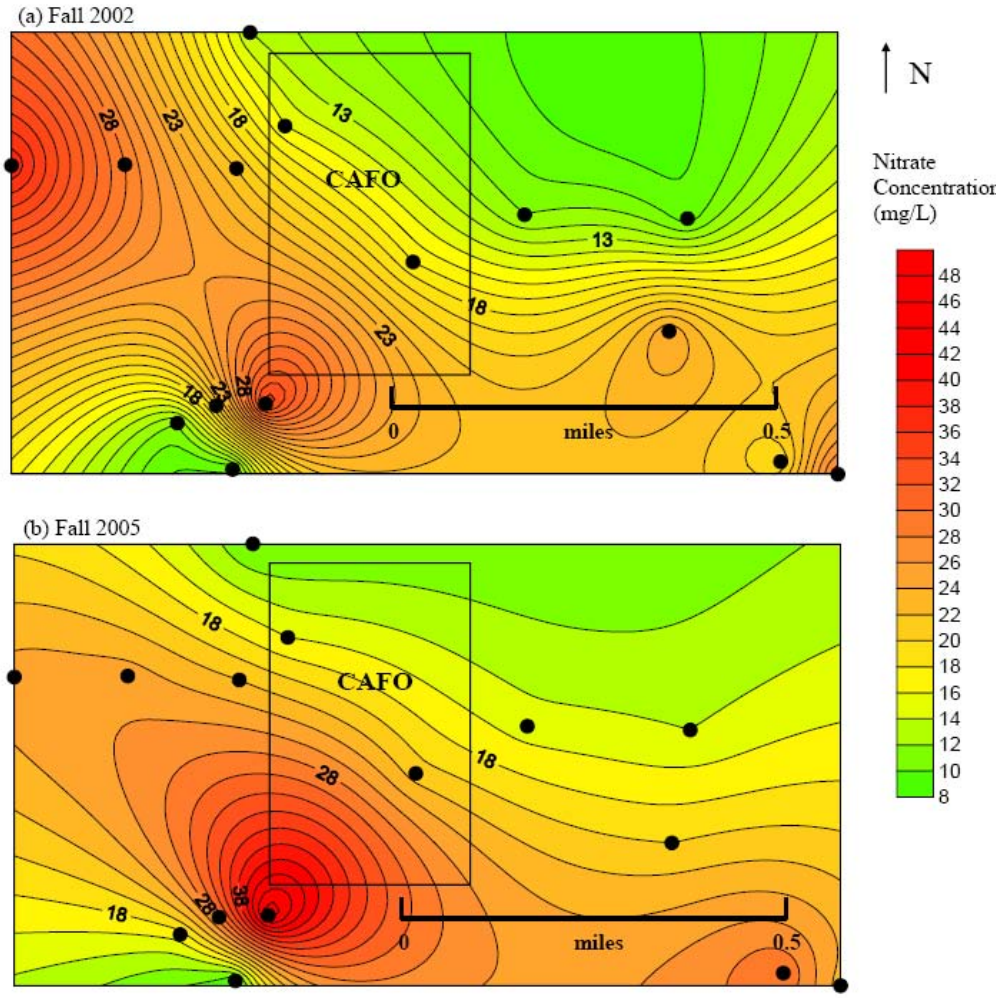


Figure 6: Map of groundwater nitrate concentration (mg/L) distribution for 2002 versus 2005 estimated from actual well concentrations. The same 15 wells (black dots) were sampled for each year. Highest nitrate concentration was localized on the southwest side of the CAFO in both years, with higher concentrations in 2005. Source: ISDA / IDEQ

Pesticides

Eight of nine domestic well samples analyzed for pesticides showed pesticide concentrations ranging from non-detect (ND) to low parts per billion (ppb) or micrograms per liter (µg/L) (Table 3). These concentrations were below state and federal standards for safe drinking water. Since none of the water samples had pesticide levels above state or federal standards, it is unlikely that they pose a hazard to human health.

Table 3: Pesticide concentrations May 2005 & November 2005.

Pesticide	Concentration (µg/L)	EPA Standard (MCL or HA) (µg/L)
Atrazine	**ND – 0.074**	**3***
Desethyl Atrazine	**ND – 0.24**	**3***
Bromacil	**ND – 0.18**	**90**
Prometon	**ND – 0.09**	**100**
Hexazinone	**ND – 0.22**	**--**
Simazine	**ND – 0.039**	**3***

* Under proposed new EPA standards, these will be regulated as one group with one combined MCL of 3 µg/L. Adding the detected level of these three pesticides together does not exceed this new standard.

Antibiotics

Two antibiotics from the sulfonamide class of antibiotics have been detected in both domestic and monitoring wells down gradient of the CAFO. Figure 7 summarizes sulfonamide concentrations detected between 2002 and 2005. Table 4 summarizes sulfonamide concentrations in 2004 and 2005. Since antibiotics in drinking water are not regulated by the US EPA, there are no regulatory standards (MCLs) for any type of antibiotic. The antibiotic contaminants are given further consideration in the text that follows (see Discussion section).

Table 4: Antibiotic concentrations December 2004 through November 2005.

Compound	Concentration (µg/L)
Groundwater samples	
Sulfamethoxazole	**ND – 0.22**
Sulfamethazine	**ND – 2.3**
Wastewater lagoons	
Total Sulfonamides	**10-42**

Steroid Hormones

The steroid hormone 17-beta estradiol (also referred to as estradiol) is commonly used in feedlot operations, and was found in private groundwater wells down gradient of the feedlot in concentrations ranging from 0.063 to 2.8 µg/L (ppb). 17-beta estradiol is naturally produced within the body by mammals. 17-beta estradiol is given to beef cattle as a growth accelerator,

usually as an implant under the skin. Estradiol in various forms is also used as a human pharmaceutical and is commonly prescribed to post-menopausal women for hormone replacement therapy.

Figure 7 summarizes 17-beta estradiol concentrations detected in the wells that were monitored between 2002 and 2005. Only monitoring well 6 (MW 6) had a detectable level of 17-beta estradiol (1.2 µg/L) in 2006, which is highlighted in Figure 7. The limit of detection for 17-beta estradiol in water using the methods described here is 0.05 µg/L.

Due to the general east-to-west groundwater gradient and the presence of houses in this direction, it is possible that other domestic wells in the area could be impacted in the future. There are no regulatory standards (MCLs) for this class of hormones in drinking water.

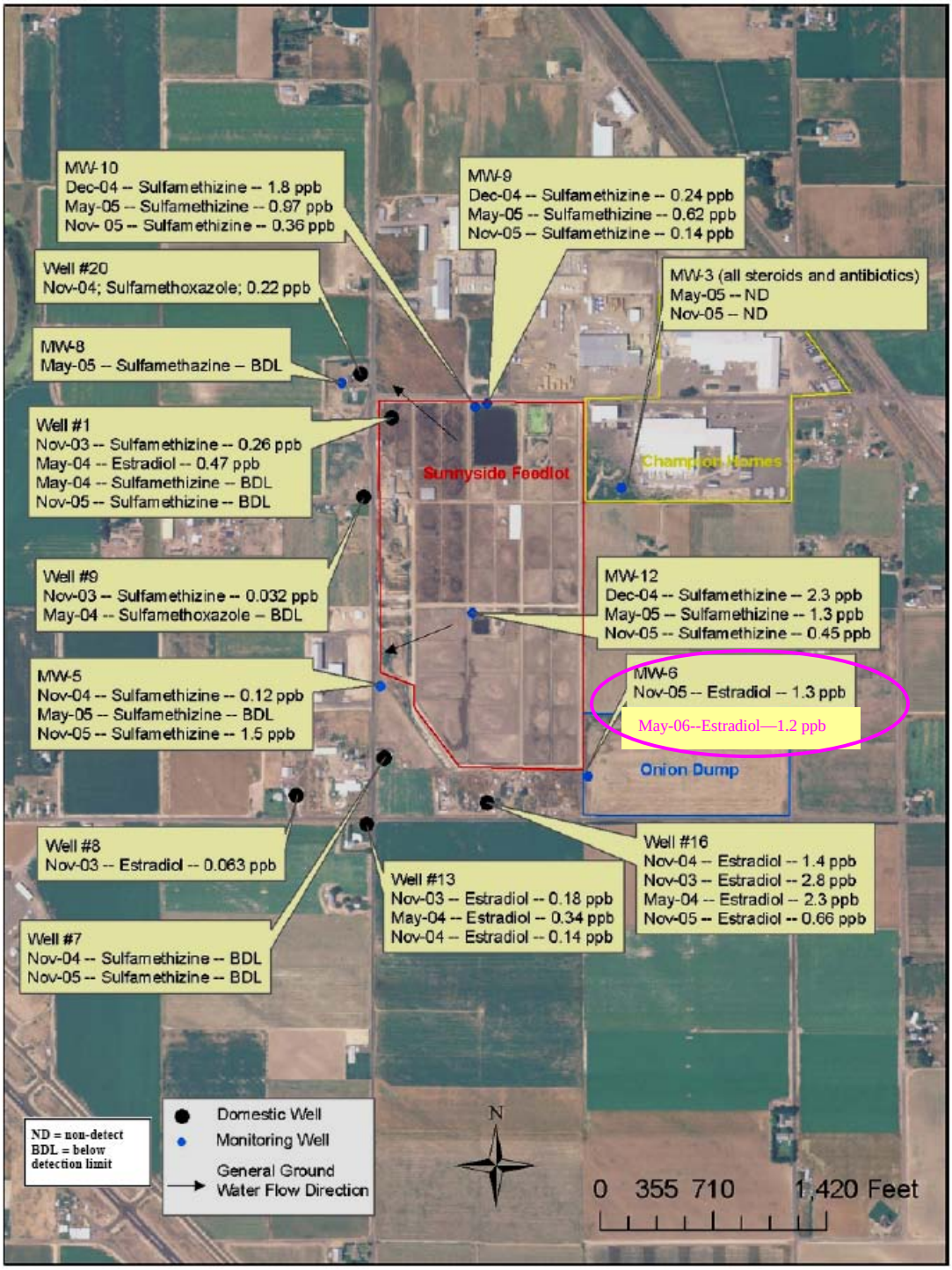


Figure 7: Antibiotic and steroid hormone groundwater concentrations, 2003-2005. MW #6 (circled) is the only well in 2006 above the limit of detection of 0.05 ppb for 17-beta estradiol, at 1.2 ppb. Source: ISDA / IDEQ.

Discussion

Risk estimates are based on highest detections of contaminants at the Sunnyside site. Estimates are generated using the assumptions listed below.
Body Weight Infant 4 kg
Body Weight Child 15 kg
Body Weight Adult 70 kg
Water Consumption Infant 0.64 L/day
Water Consumption Child 1 L/day
Water Consumption Adult 2 L/day

Nitrates

Nitrate is a normal component of the human diet. A typical daily intake by an adult in the United States is about 75,000 µg/day (about 200-300 µg/kg/day). Of this, over 85% comes from the natural nitrate content of vegetables such as beets, celery, lettuce and spinach. The contribution from drinking water is usually quite small for adults (about 2-3% of the total) (NAS 1981). The contribution from drinking water for children is usually much greater. Elevated nitrate levels interfere with infants' ability to transport oxygen from the lungs to the tissues. When it happens it is called methemoglobinemia or blue baby syndrome. This can be an acute condition which causes the child's health to deteriorate rapidly over a period of days. Symptoms include shortness of breath, blueness of the skin and lips, weakness, rapid pulse, and rapid breathing (ATSDR, 2000).

From the early clinical signs of methemoglobinemia due to nitrate consumption in infants, it was determined that the "lowest observed adverse level" (LOAEL) was in a range of 1,800 – 3,200 µg/kg/day. This dose was based on nitrate water concentrations that ranged from 11 -20 ppm. Studies also showed that 10 mg/L (1,600 µg nitrogen/kg/day) is a "no observed adverse effect level" (NOAEL) for nitrate ingestion in infants (EPA 2007). EPA has incorporated the10mg/L value into their oral reference dose (RfD), which is defined as an amount of chemical below which health effects are not expected. EPA's MCL for nitrate in water is also set at 10 mg/L. The health-based NOAEL value of 10 mg/L for nitrate in water is generally considered an upper limit for infant water consumption. It is also generally considered prudent public health practice to restrict infant consumption of nitrate-contaminated water when levels exceed 10 mg/L.

The available data show that nitrate levels in Sunnyside CAFO-area monitor wells routinely exceed MCL and thus also exceeded the associated NOAEL and RfD. Approximately 2/3 of wells tested exceeded the MCL and thus exceeded the RfD. Because most of the area wells exceed the health-based values for nitrates in water, ATSDR has determined that infants should not drink water from area wells. This determination leads to a precautionary recommendation that holds unless the specific well has been tested and found to contain acceptable levels of nitrates. Due to ongoing education efforts in the area, it is believed that area residents are not using the contaminated wells for drinking water. However, it is uncertain whether area residents are using the contaminated well water for food preparation. Levels of nitrate detected are not expected to pose a health risk to adults or to older children.

Antibiotics

Sulfamethoxazole and sulfamethazine were also found in some of the area wells. However, there are no health-based guidelines to follow when evaluating the possible effects of those contaminants when consumed in drinking water. Therefore, a review of the available toxicological information on the antibiotics and Estradiol was conducted. The pathway that would likely confer the largest exposure dose is ingestion. Therefore, the following evaluation is focused on the ingestion pathway.

The exact human risks of lifetime exposure to low levels of sulfamethoxazole and sulfamethazine are unknown, as there are no human studies that document such exposure. However, based on available data from the U.S. Food and Drug Administration (FDA), there is no reason to believe that lifetime exposure to these 'sulfa' drugs at this concentration will cause any adverse health effects. It is possible that this exposure could contribute to bacterial resistance to antibiotic therapy in individuals exposed for a lifetime, but there are no data to support or refute this hypothesis. Although some individuals are particularly sensitive to side effects from sulfa drugs, there is no evidence to suggest sensitivity will occur at the level present in wells at this site.

The FDA has established a Maximum Recommended Therapeutic Dose (MRTD) for many pharmaceuticals. MRTDs establish the recommended maximum amount of a drug to be given to a patient without causing adverse health effects. These MRTDs are defined in units of milligrams per kilogram of body weight per day (mg/kg/day). Having MRTDs allows for the comparison of doses on a per body weight basis, and facilitates evaluation of risk, particularly risk to children.

Sulfamethiazine (synonym: sulfamethazine) is not currently approved by the FDA in formulation for humans, but has been in the past. The MRTD for sulfamethiazine is 50 mg/kg/day (FDA, February 2006). Using standard assumptions for body weight and liters of water per day, at the highest detection in groundwater, 2.4 µg/L, adults would receive a dose of 0.000068 mg/kg/day, and children would receive 0.00016 mg/kg/day. This difference between the MRTD for sulfamethiazine and the estimated exposure dose is very large. Children would receive a dose that is more than 300,000 times lower than the MRTD and adults would be exposed to a dose that is over 735,000 lower than the MRTD for adults.

The FDA does not list an MRTD for sulfamethoxazole, however it has approved a maximum formulated adult dosage of 1000 mg to be taken twice daily for urinary tract infection (FDA, January 2007: Micromedex, accessed January 2007). Assuming a body weight of 70 kg for an adult, this equates to approximately 28.5 mg/kg/day. At a sulfamethoxazole drinking water concentration of 0.44 µg/L, adults would receive a dose of sulfamethoxazole of 0.0000126 mg/kg/day, and children a dose of 0.000030 mg/kg/day. For this exposure scenario, using the exposure estimate for children, the difference between the estimated exposure dose and the MRTD for sulfamethoxazole is approximately a factor of one million.

It must be noted, however, that antibiotic therapeutic agents are typically taken for a short period of time (e.g., 10 days to 2 weeks). The effects of chronic exposure to very low levels of sulfamethoxazole and sulfamethiazine, if any, are unknown, but it is reasonable to expect that there is a threshold for effects, and that exposures below this threshold, even exposures of chronic duration, should be without adverse health effects.

Steroid Hormones

17-beta estradiol was detected in several area wells. 17-beta estradiol is potent steroid hormone that is naturally produced in both male and female animals. Estrogens are widely used as growth promoters in cattle and are also used as therapeutic agents in humans. Estradiol is typically at much higher circulating levels in adult females than males, and levels in females can vary widely according to reproductive and estrus status. Estradiol production in humans is approximately 48 µg/day for adult males and ranges between approximately 82-690 µg/day for adult females, with the highest levels found in pre-ovulatory females (Hoffman and Evers, 1986) (Table 5). The levels of estradiol in children is a matter of some debate; however the newest data available indicate that estradiol levels in children are much lower than the levels previously accepted over the last several decades. Results from the newest and most sensitive methodology indicate that the range of mean estrogen production in boys from onset of puberty to the end of puberty is approximately 0.22-2.3 µg/day and in girls from onset of puberty to the end of puberty is approximately 0.87-26 µg/day (Janfaza et al. 2006; Andersson and Skakkebaek 1999), though in some children production can be far lower than this.

Based on the differences in exposure scenarios and the possible effects in different receptors, two evaluation approaches have been taken for the assessment of estradiol. First is an approach that is focused on adults. This approach considers adult estrogen levels, and levels of estrogen used for therapeutic purposes. The second approach evaluates the estimated exposures and possible effects on children.

Exposure Scenario for Adult Male and Female
At the highest detection level of 1.4 µg/L for estradiol in drinking water, an adult weighing 70 kg would receive a dose of 2.8 µg/day. Adult men produce approximately 48 µg estradiol/day and adult women produce approximately 82-690 µg estradiol/day (Table 5). These naturally produced levels of estrogen are at least ten times more that the highest amount estimated to be consumed in contaminated water from wells in the Sunnyside area. Given the levels of naturally produced estrogen in both males and females, it is unlikely the additional estrogen ingested in the contaminated drinking water would exert a measurable effect.

17-beta estradiol was approved in 1975 for estrogen replacement therapy (ERT) for post-menopausal symptoms in women, and it continues to be approved for this use in humans. It has also been used as a growth promoter in animals for at least as long. When used for human ERT, oral doses of estradiol are in the range of approximately 0.6 to 1 mg/day (based on information from two human estradiol pharmaceutical manufacturers (makers of the trade names Estrace and Gynodiol). A prescribed recommended dose (for 1 mg/day), when normalized for body weight, is 0.014 mg/kg/day, assuming an adult body weight of 70 kg. Using the highest detection level

of 1.4 µg/L for estradiol in drinking water, an adult female (assuming 70 kg body weight) would receive a dose of 2.8 µg/day. The MRTD for estradiol is 0.5 mg/kg/day. At 1.4 µg/L in drinking water, doses to adult females would be 0.00004 mg/kg/day In this exposure scenario, estradiol doses to adult women due to ingestion of contaminated drinking water are 5,000-10,000 times lower than the MRTD. Therefore, it is unlikely the additional estrogens that would be consumed in the contaminated drinking water would exert a measurable effect.

Table 5: Estimated mean daily estradiol production in humans.

Subject		Estradiol Production (µg/day)
Women		82-690
Men		48
Girls		
	Stage 1	0.87
	Stage 2	3.7
	Stage 3	12
	Stage 4	14
	Stage 5	26
Boys		
	Stage 1	0.22
	Stage 2	0.38
	Stage 3	1.3
	Stage 4	1.9
	Stage 5	2.3

Source: Adults--Hoffman and Evers, 1986. Children--Janfaza et al. 2006; Andersson and Skakkebaek 1999.
Stages refer to stages of development in puberty, 1=youngest, 5=oldest (end of puberty).

Exposure Scenario for Children

Both the U.S. Food and Drug Administration (FDA) and the World Health Organization (WHO) assume a natural production of estradiol of 6 µg/day in young boys (US FDA 1999). This level has been scrutinized in recent years, and some recent studies suggest the natural estradiol production in boys may be far lower than 6 µg/day. Initial reports, using a super-sensitive methodology (Klein et al. 1994; Andersson and Skakkebaek, 1999; Aksglaede et al. 2006), estimate estradiol production in young boys to be between 0.04-0.1 µg/day. The newest clinical study of estradiol levels in children (Janfaza et al. 2006) provided a more representative view by testing 800+ children across a broader age range in three different states. Using the calculations applied by Andersson and Skakkebaek (1999) to the results of Janfaza et al. (2006), the mean estradiol production levels in boys is 0.22-2.3 µg/day (Table 5). Many boys had levels as low as, or lower than, 0.01 µg/day (which is the limit of detection). Boys' mean estradiol levels ranged from 0.22-2.3 µg/day. The lowest individual value of 0.01 µg/day is 600 times lower than the natural estrogen production level assumed by WHO and FDA. The study of 800+ children indicates that prepubertal girls had mean estradiol levels ranging from 3.7-26 µg/day. Some of the girls in this study also had undetectable estradiol levels (Janfaza et al. 2006)).

When considering the estradiol production rate assumed by the WHO and the FDA, the estimated 2.8 µg/day dose of estradiol, consumed in drinking water, increases the daily internal estradiol exposure to children by approximately 30 %. When considering the more recent estimates of estradiol production in children (i. e., the lowest estimates), the 2.8 µg/day dose of estradiol obtained from drinking the contaminated water increases the estradiol exposure to children by at least 20 times, and possibly as much as 600 times. It is biologically plausible that such increased exposures to estradiol could result in clinically measurable effects in children.

The FDA's guideline for natural sex steroids used in food-producing animals states "that no physiological effect will occur in individuals chronically ingesting animal tissues that contain an increase of endogenous steroid equal to 1% or less of the amount in micrograms produced by daily synthesis in the segment of the population with the lowest daily production" (U.S. FDA 1999). In the case of 17-beta estradiol, boys who have not reached puberty produce the least estradiol with estimates ranging from 6 µg/day (FDA and WHO assumption) to 0.01 µg/day (Klein et al. 1994; Janfaza et al. 2006), the most recent estimate based on analysis using a super-sensitive methodology. It can be assumed that the same intake via drinking water would also be acceptable. Thus, an acceptable intake level, using the highest estradiol production rate, would be 0.06 µg/day. This estrogen level was exceeded by all of the reported estrogen levels in the monitored wells. It follows that all detectable levels of estradiol found at or near the CAFO also exceed the acceptable levels that are derived from the estimates based on the lowest estrogen production rates in children.

Another point to consider is that the analytical limit of detection (LOD) for the method that detects estradiol in drinking water is 0.05 µg/L, This means that any sample below this level is considered 'non-detectable', even if some amount of estradiol is present. If the FDA/WHO guideline is used in the risk analysis, this LOD is acceptable for predicting risk since it is below the level of concern. If the other studies are used in the risk analysis, the LOD of 0.05 µg/l is far higher than the level of concern in water of 0.0001 µg/L. This means that there may be estradiol

above an acceptable threshold in water but scientists are not able to detect these levels using the current laboratory methods.

Uncertainties

Our confidence in the evaluations presented in this Health Consultation is dependent on the uncertainties and limitations associated with each of the specific contaminants. For instance, the conclusions regarding the nitrates are considered solid; however, we have less confidence in the data when evaluating antibiotics and estradiol. These uncertainties are due to a lack of information that is needed to answer key questions. Those questions center on the ability to predict exposures and the possible effects of the antibiotics and estradiol in adults and children. Despite the uncertainties associated with each contaminant, it is noted that for all of the assessments, the highest concentration of a given contaminant is used to estimate exposures. This manipulation in our exposure assessment produces a "high end", or perhaps a "worst case", exposure scenario. This manipulation also tends to overestimate versus underestimate exposures. Thus, in an effort to construct conservative exposure assessments, we have used the highest detected concentrations of the specific contaminants.

Our confidence in the assessments and the uncertainties and limitations associated with the specific contaminants are discussed below.

Uncertainties Associated with Nitrates. The exposure assessments concerning the nitrate water contaminants are based on historical knowledge, standardized analyses, and established, health-based guidelines. Therefore, the recommendations regarding the nitrates are considered definitive. Further, the recommendations are consistent with precedents for public health practice.

Uncertainties Associated with the Antibiotics. Available evidence indicates that the low levels of the two sulfa antibiotics found in well water are not likely to exert a direct, adverse effect on humans. An important uncertainty is the lack of data about allergic reaction dose-response to very low levels of sulfa antibiotics. However, due to the extremely low levels of sulfa drugs present, it is believed that no reaction would occur in people with sulfa drug allergies upon exposure to the levels of sulfamethoxazole and sulfamethiazine found in water samples at this site. It is also important to note that there is evidence suggesting that antibiotic contamination can alter microbial communities in soil, and there is evidence suggesting that antibiotics in soil can selectively favor the development of antibiotic resistant microbes (Tomasz 2006). In addition, bacteria can transfer resistance genes to bacteria that are human pathogens (Amabile-Cuevas 2003). The potential of such events having occurred in the Sunnyside area, or occurring in the future, is unknown. Regardless of the likelihood of such events, it is reasonable to implement a protective public health recommendation that eliminates the ingestion of the contaminated water.

Uncertainties Associated with Estradiol. Numerous and significant uncertainties are associated with our evaluation of the estradiol exposures, and much of the concern related to estradiol is for exposed children. Given the current data gaps, a rigorous assessment of the effects of the

estradiol found in the Sunnyside area wells is not possible. Although the data gaps severely limit the strength of the conclusions that can be drawn from the data, there are several aspects of the estradiol exposure scenario that deserve discussion.

Contributing to our likely over-estimation of the estradiol exposures is the fact the hormone was detected in several wells in 2004-2005, but was found in only one well in 2006. For the assessments described in this Health Consultation, the estradiol level found in the one well in 2006 was used to evaluate the community exposures for the general area. The absence of estradiol in all but one well in the latest test year may indicate that there in a natural reduction of the hormone in the area groundwater. The biological half-life of estradiol in surface waters is in the range of 10 days (Shore & Shemesh 2003). Probably due to its rarity, no reports of the biological half-life of estradiol in groundwater were found in the literature.

The detection limits for the analyses that generated the estradiol data considered in this health consultation are approximately 0.05 µg/L. This limit of detection would be acceptable for all but a very few specific environmental contaminants. However, there are unanswered questions about whether that limit of detection is sensitive enough to permit an evaluation of estrogenic compounds in drinking water (also see the discussion of exposures to children that is presented below).

Other factors that contribute to the uncertainties associated with the estradiol exposure assessments include the effect of first-pass metabolism. Oral doses of estradiol undergo rapid biotransformation by first-pass hepatic metabolism. This biotransformation can effectively reduce an oral estradiol dose by as much as 90-98 % (O'Connell 1995). The first-pass metabolism produces estrone, a less potent estrogenic hormone, and subsequent metabolic activities prepare the estrone for urinary excretion. It is likely that the first pass-metabolism of estrogen in the hormone-contaminated drinking water reduces the bioavailable concentrations of estradiol obtained from the drinking water. Such an event would effectively reduce the exposure estimates presented in this health consultation. It is not known to what extent the estrogen metabolites, produced after first-pass metabolism of a drinking water dose, may exert an estrogenic effect in adult males or females. Further, the capacity for children to biotransform an oral dose of estradiol, and thereby reduce an estradiol exposure, is not known.

An overarching issue with the assessment of the estradiol contamination is the data gaps in our understanding of the effect that very low doses of environmental estrogens may have, through long or short term exposures, on humans. A recent study documented very low production of estradiol in 800+ children at various stages of pre-puberty through puberty (Janfaza et al. 2006).

However, there is currently no regulatory agency consensus for a reference range of estradiol in prepubescent children. Given this limitation, confidence in any assessment of the effect of drinking water doses of estradiol is limited. Given the arguments presented by Andersson and Skakkebaek (1999) and Aksglaede et al. (2006), environmental exposures to estrogens (in food or water) should be targeted for further research. Research is also needed to define the hormone production rates in children and to establish an analytical method, with an appropriate detection limit, that will provide the data needed to answer the questions that are currently unanswerable.

In summary, the assessment of the nitrate contaminants are solid and drive the public health recommendation to avoid drinking the contaminated water. The uncertainties in our evaluations, and the associated concerns, particularly for the Estradiol exposures to children, reinforce the recommendation of not using the contaminated water as a drinking water source.

Natural Degradation of Contaminants Over Time

Several studies show that hormones and antibiotics in the environment rapidly degrade and can drop to below detection levels within a week to a few months (Casey et al. 2003; Kay et al. 2004; Shore and Shemesh 2003). Based on these findings, it is anticipated that existing antibiotics and steroids found in and near the CAFO site will naturally degrade with time, and will cease to be a concern, provided there is no other source of antibiotics and steroid hormones in the area. However it is noted that estradiol in MW 6 showed no significant change over the approximate seven-month interval between sampling events (November 2005-May 2006). If one accepts the premise that hormones in the environment are subject to rapid degradation, the continued high level of 17-beta estradiol in MW 6 is problematic. The apparent stable levels of estradiol in MW 6 could be due to an as-yet undetected source. Alternatively, the geochemistry and/or microbial communities in the area may not facilitate rapid degradation processes. Regardless of the mechanism(s) at play, the reason(s) for this continued elevation of estradiol warrants further investigation and continued monitoring.

There are many potential sources for nitrates in the area. These potential sources include the agricultural application of nitrogen-based fertilizers, septic systems, and natural soil degradation processes. Based on the expected presence of various sources and the persistence of nitrates in groundwater, it is reasonably anticipated that nitrates will continue to contaminate groundwater and wells in this area. Therefore, there should be continued monitoring of area wells for nitrates.

Children's Health Considerations

The unique vulnerabilities of infants and children demand special emphasis in communities faced with contamination in their environment. Children are at greater risk than adults from certain types of exposures to hazardous substances. Their lower body weight and higher intake rate results in a greater dose of hazardous substance per unit of body weight. The developing body systems of children can sustain damage if toxic exposures occur during critical growth stages. Most importantly, children depend completely on adults for risk identification and management decisions, housing decisions, and access to medical care. The contaminants found in the well water in the area of the Sunnyside CAFO can have specific and significant effects on infants and children. In the construction of this health consultation, we have paid particular attention to estimating and addressing those exposures to children. Our analyses have generated concerns about the estimated exposures to children in the area of the Sunnyside CAFO, and our recommendation to restrict usage of contaminated water is primarily based on those concerns.

Conclusions

Ingestion of contaminants through drinking well water is the primary pathway of concern for those living near the Sunnyside CAFO in Weiser. Inhalation can also potentially lead to exposure, though this exposure is not expected to be of sufficient duration or frequency to be a serious concern.

1. Nitrates: Based on available data, a public health hazard exists from estimated exposure of infants to well water above the MCL of 10 mg/L, which equates to the infant RfD of 1,600 µg/kg/day. Approximately 2/3 of wells tested exceeded the MCL and thus exceeded the RfD for nitrates in drinking water.

2. Pesticides: Based on available data, no apparent public health hazard exists from estimated exposure to pesticides detected in well water.

3. Sulfonamide Antibiotics: Based on available data, no apparent public health hazard exists from estimated exposure to sulfonamide antibiotics in well water, though uncertainties exist.

4. 17-beta estradiol: Based on available data, an indeterminate public health hazard exists from estimated exposure of children and teenagers to detectable levels of 17-beta estradiol in well water, in light of the many uncertainties that exist. Exact effects of children's exposure to this level of 17-beta estradiol are not known.

Recommendations

The following recommendations should be considered:

1. No one should consume water from wells next to or downgradient of the CAFO due to the know hazard of nitrate contamination and the uncertainty about the safety of estradiol concentrations found in these wells.

2. It is suggested that other wells down gradient (west, south, southwest) of the CAFO be tested for nitrates and 17-beta estradiol. If a well tests over 10 mg/L nitrates or tests positive for 17-beta estradiol, residents should cease consuming this water.

3. The Onion Dump (SE of the CAFO) should be inspected for potential remaining source(s) of 17-beta estradiol.

Public Health Advice/Public Health Action Plan

Completed Actions
The following is a list of actions that have already been completed.

1. ISDA and IDEQ have participated in the Weiser Water Roundup for the last 2 years and distributed posters to the public about the Sunnyside water project.

2. Homeowners were sent letters by ISDA after each sampling event with their data and information about nitrate levels.

3. All technical reports were sent to homeowners and agencies. Press releases were also put out for each report.

4. ISDA has presented Sunnyside water project information to the Weiser Nitrate Priority Planning Committee in Weiser several times. ISDA, IDEQ and BCEH presented information jointly at the last Weiser Nitrate Priority Planning Committee meeting in December 2006.

5. ISDA has worked in conjunction with Southwest District Health to send out postcards to residents in the Weiser Flats and Sunnyside Project areas with nitrate information.

6. There is continuing surveillance of domestic and monitoring wells in the area by ISDA and IDEQ.

Planned Actions

1. ATSDR and BCEH will provide the findings of this health consultation to the public.

2. BCEH will work with US EPA and IDEQ to have any remaining ponds or lagoons on the CAFO site drained and the water disposed of properly off-site.

3. BCEH will work with ISDA and IDEQ to have the Onion Dump (SE of the CAFO) inspected for potential remaining source(s) of 17-beta estradiol if future well monitoring shows continued levels above the detection limit.

4. BCEH will work with Southwest District Health to provide clear notification to residents in the entire Sunnyside area. The message is that infants, particularly those less than 9 months old, should not be allowed to drink well water from this area, and infant formula or other foods should not be prepared for infants using well water from this area.

5. BCEH will work with Southwest District Health to ensure an alternative source of drinking water is available to residents whose wells are affected. BCEH will assist IDEQ state and local offices in their implementation of the Idaho Groundwater Quality Plan (IDEQ 1996).

Authors of Report

Kai Elgethun PhD, MPH
State Public Health Toxicologist
Health Assessor
Idaho Division of Health
Bureau of Community and Environmental Health

Clement Welsh PhD
Deputy Director
Division of Regional Operations
Agency for Toxic Substances and Disease Registry

Reviewers of Report

Richard Kauffman, M.S.
Senior Regional Representative, Region 10
Division of Regional Operations
Agency for Toxic Substances and Disease Registry

Jim Vannoy, MPH
Program Manager
Idaho Division of Health
Bureau of Community and Environmental Health

Elke Shaw-Tulloch, MHS
Bureau Chief
Idaho Division of Health
Bureau of Community and Environmental Health

Robert B. Knowles, M.S. REHS
Technical Project Officer, DHAC, CAPEB
Division of Health Assessment and Consultation
Agency for Toxic Substances & Disease Registry

References

Aksglaede L, Juul A, Leffers H, Skakkebaek NE and AM Andersson. The sensitivity of the child to sex steroids: possible impact of exogenous estrogens. Human Repro Update 12: 342-349 (2006).

Amabile-Cuevas CF. New antibiotics and new resistance: in many ways, the fight against antibiotic resistance is already lost; preventing bacterial disease requires thoughtful new approaches. American Scientist 91:138 (2003).

Andersson AM and NE Skakkebaek. Exposure to exogenous estrogens in food: possible impact on human development and health. European J Endocrinol 140: 477-485 (1999).

ATSDR. Public Health Assessment. City of Perryton Well No.2 (aka Perryton Water Well Number 2), Perryton, Ochiltree County, Texas. Prepared by the Texas Department of Health under a cooperative agreement with the ATSDR. 2000.

ATSDR Case Studies in Environmental Medicine. Nitrate/Nitrite Toxicity. Revised January 2001.

ATSDR. Interaction Profiles for Toxic Substances. Interaction Profile for Atrazine, Deethylatrazine, Diazinon, Nitrate, and Simazine , August 2006. Available online: http://www.atsdr.cdc.gov/interactionprofiles/ip10.html.

Bay K, Andersson AM and NE Skakkebaek. Estradiol levels in prepubertal boys and girls—analytical challenges. Int J Andrology 27: 266-273 (2004).

Caruso-Nicoletti M, Cassorla F, Skerda M, Ross JL, Loriaux DL and GB Cutler Jr. Short term, low dose Estradiol accelerates ulnar growth in boys. J Clin Endocrinol Metab 61: 896-8 (1985).

Casey FX, Larsen GL, Hakk H and J Simunek. Fate and transport of 17beta-Estradiol in soil-water systems. Environ Sci Technol. Jun 1;37(11):2400-9, 2003.

Hoffman B and P Evers. In *Drug Residues in Animals*. A.G. Rico (Ed.),111-146. New York: Academic Press, 1986.

Idaho Department of Environmental Quality. Idaho Groundwater Quality Plan. Boise, 1996.

Janfaza M, Sherman TI, Larmore KA, Brown-Dawson J and KO Klein. Estradiol levels and secretory dynamics in normal girls and boys as determined by an ultrasensitive bioassay: a 10 year experience. J Pediatr Endocrinol Metab 19: 901-9 (2006).

Kay P, Blackwell PA and AB Boxall. Fate of veterinary antibiotics in a macroporous tile drained clay soil. Environmental Toxicology and Chemistry: No. 23, pp. 1136–1144, 2004.

Klein KO, Baron J, Colli MJ, McDonnell DP, Cutler GB Jr. Estrogen levels in childhood determined by an ultrasensitive recombinant cell bioassay. J Clin Invest. 94:2475-80 (1994).

Kuhnz W, Gansau C and Mahler M. Pharmacokinetics of Estradiol. Free and total estrone in young women following a single intravenous and oral administration of 17-Estradiol. Arzneimittelforschung 43: 966-73 (1993).

Micromedex® Healthcare Series. Thomson Micromedex. http://www.thomsonhc.com; accessed January 30, 2007.

National Academy of Sciences (NAS). 1981. The health effects of nitrate, nitrite and N-nitroso compounds. National Academy Press, Washington, DC.

NSF/ANSI Standards for Drinking Water Treatment. Available online: http://www.nsf.org/business/drinking_water_treatment/standards.asp?program=DrinkingWatTre Accessed October 10 2006.

O'Connell MB. Pharmacokinetic and pharmacologic variation between different estrogen products. J Clin Pharmacol 35(9 Suppl):18S-24S (1995).

Shore LS and M Shemesh. Naturally produced steroid hormones and their release into the environment. Pure Appl. Chem. 75: 11-12, pp. 1859-1871, 2003.

Soto, A.M., J.M. Calabro, N.V. Prechtl, A.Y. Yau, E.F. Orlando, A. Daxenberger, A.S. Kolok, L.J. Guillette, B. le Bizec, I.G. Lange, and C. Sonnenschein. Androgenic and estrogenic activity in water bodies receiving cattle feedlot effluent in eastern Nebraska, USA. Environ. Health Perspect. 112:346–352, 2004.

Tomasz A. Microbiology: Weapons of Microbial Drug Resistance Abound in Soil Flora Science 311: 342 – 343 (2006).

U.S. Environmental Protection Agency (EPA). Updated January 25, 2007. Safe Drinking Water Fact Sheet for Nitrate. Available online: http://www.epa.gov/iris/subst/0076.htm

U.S. Environmental Protection Agency (EPA). Drinking water health advisories. October 18, 2006. Available online: http://www.epa.gov/waterscience/criteria/drinking/

U.S. Environmental Protection Agency (EPA). Setting standards for safe drinking water. February 28, 2006. Available online: http://www.epa.gov/safewater/standard/setting.html.

U.S. Environmental Protection Agency (EPA). Setting standards for safe drinking water. November 28, 2006. Available online: http://www.epa.gov/safewater/standard/setting.html.

U.S. Food and Drug Administration (FDA). Guideline 3, Part 2: Guideline for toxicological testing, 1-5, 1999. Available online: www.fda.gov.

U.S. Food and Drug Administration (FDA). Orange Book of Approved Drug Products, current through December 2006. Available online: http://www.fda.gov/cder/ob/.

U.S Food and Drug Administration (FDA). Maximum Recommended Therapeutic Dose (MRTD) Database, February 6, 2006. Available online: http://www.fda.gov/Cder/Offices/OPS_IO/MRTD.htm#S.

U.S. Food and Drug Administration (FDA), Center for Drug Evaluation and Research, Office of Drug Information. Telephone communication, January 30, 2007.

Certification

This health consultation, an Evaluation of Antibiotic, Steroid Hormone & Nitrate Compounds in Groundwater near a Confined Animal Feeding Operation (CAFO) in the Sunnyside Area, Weiser, Washington County, Idaho, was prepared by the Idaho Division of Health (IDOH) under a cooperative agreement with the federal Agency for Toxic Substances and Disease Registry (ATSDR). It was completed in accordance with approved methodologies and procedures existing at the time the health consultation was initiated. Editorial review was completed by the Cooperative Agreement partner.

Robert B. Knowles, M.S. REHS
Technical Project Officer, DHAC, CAPEB
Division of Health Assessment and Consultation
Agency for Toxic Substances & Disease Registry

Alan W. Yarbrough, M.S.
Team Lead, DHAC, CAPEB
Division of Health Assessment and Consultation
Agency for Toxic Substances & Disease Registry

Appendix A: Calculated Exposure Doses and Assumptions

Nitrates

Parameter	Value	Units	Comments
Nitrate (measured as nitrogen) Concentration MCL	10	mg/L	US EPA Maximum Contaminant Level for Drinking Water
Ingestion Rate—Adult	2	L/day	
Ingestion Rate—Child	1	L/day	
Ingestion Rate--Infant	0.64	L/day	
Body Weight--Infant	4.5	kg	
NOAEL	10	mg/L	Clinical signs of methemoglobinemia in infants
LOAEL	11-20	mg/L	Clinical signs of methemoglobinemia in infants
RfD	1600	µg/kg/day	Based on NOAEL consumed by infant
Health outcome considered			Methemoglobinemia

Sulfonamides

Parameter	Value	Units	Comments
Sulfamethoxazole Max Prescribed Dose	1000	mg	Every 12 hours for 10-14 days
Sulfamethoxazole Max Dose in Well Water	0.22	µg /L	
Ingestion Rate—Adult	2	L/day	
Ingestion Rate—Child	1	L/day	
Body Weight--Adult	70	kg	
Body Weight--Child	15	kg	Approx. 5 years old
Sulfamethoxazole MRTD	N/A	mg/kg/day	US FDA Maximum Recommended Therapeutic Dose
Sulfamethiazine MRTD	66.7	mg/kg/day	US FDA Maximum Recommended Therapeutic Dose
Health outcome considered			Kidney function

SI (µg/day) = WC (µg /L) x IR (L/day)

$$SD\ (mg/kg/day) = \frac{[SI\ (\mu g\ /day) \times 0.001\ (\mu g\ \text{to}\ mg)]}{BW\ (kg)}$$

SI = Sulfonamide Ingestion
SD = Sulfonamide Dose
WC = water concentration
IR = ingestion rate
BW = body weight

Estradiol

Table 1: FDA/WHO Calculations

Parameter	Value	Units	Comments
17-beta estradiol Prescribed Dose	1	mg	Every 24 hours for prolonged period
17-beta estradiol Max Dose in Well Water	1.4	µg /L	
Ingestion Rate—Adult	2	L/day	
Ingestion Rate—Child	1	L/day	
Body Weight--Adult	70	kg	
Body Weight--Child	15	kg	Approx. 5 years old
17-beta estradiol MRTD	0.5	mg/kg/day	US FDA Maximum Recommended Therapeutic Dose
Chronic Meat Consumption Steroid Guideline Safety Factor (CMCSGSF)	≤1	% of naturally-produced steroid hormone below which no effect is expected	Multiply by lowest daily production for most sensitive population (prepubertal boys)
Natural 17-beta estradiol Production—Prepubertal boys	6	µg /day	FDA and WHO assumption of 17-beta Estradiol production
Health outcome considered			Accelerated bone growth

EI (µg /day) = WC (µg /L) x IR (L/day)

$$\text{ED (mg/kg/day)} = \frac{\text{[EI (µg /day) x 0.001 (µg to mg)]}}{\text{BW (kg)}}$$

CMCSG (µg /day) = CMCSGSF (%) x NEP (µg /day)

EI = Estradiol Ingestion
ED = Estradiol Dose
WC = water concentration
IR = ingestion rate
BW = body weight
CMCSG = FDA Chronic Meat Consumption Steroid Guideline
CMCSGSF = FDA Chronic Meat Consumption Steroid Guideline Safety Factor
NEP = FDA/ WHO natural 17-beta estradiol production

Table 2: Calculations using recent data

Parameter	Value	Units	Comments
17-beta estradiol Max Dose in Well Water	1.4	µg /L	
Ingestion Rate—Adult	2	L/day	
Ingestion Rate—Child	1	L/day	
Chronic Meat Consumption Steroid Guideline Safety Factor (CMCSGSF)	≤1	% of naturally-produced steroid hormone below which no effect is expected	Multiply by lowest daily production for most sensitive population (prepubertal boys)
Lowest circulating 17-beta estradiol in boys (same as limit of detection)	0.07	Pmol/L	N=425 boys; some fraction were below this level, which was the LOD. Janfaza et al 2006.
Molecular wt of 17-beta estradiol	272.39	g/mol	Needed to convert moles to mass
Adult Metabolic clearance rate of 17-beta estradiol	1350	L/day	Needed to determine daily production from circulating level; Longcope et al. 1968
Child Metabolic clearance rate of 17-beta estradiol	540	L/day	Calculated using body surface area comparison of adult to child, ratio = 0.4. Andersson and Skakkebaek 1999
Lowest Natural 17-beta estradiol Production — Prepubertal boys	0.01	µg /day	Based on Janfaza et al. value of 0.07 pmol/L.

EI (µg /day) = WC (µg /L) x IR (L/day)

RL (µg /day) = CMCSGSF (%) x LNEP (µg /day)

EI = Estradiol Ingestion
WC = water concentration

IR = ingestion rate
RL = risk level
CMCSGSF = FDA Chronic Meat Consumption Steroid Guideline Safety Factor
LNEP = calculated lowest natural 17-beta estradiol production using recent data

Appendix B: Glossary

Acute Occurring over a short time.

Antibiotic A drug that is used to treat or prevent bacterial infection in humans or animals. Livestock are given antibiotics to prevent disease while they are kept in CAFOs to increase weight gain before slaughter.

Agency for Toxic Substances and Disease Registry (ATSDR)
The principal federal public health agency involved with hazardous waste issues, responsible for preventing or reducing the harmful effects of exposure to hazardous substances on human health and quality of life. ATSDR is part of the U.S. Department of Health and Human Services.

Aquifer An underground formation composed of materials such as sand, soil, or gravel that can store and/or supply groundwater to wells and springs.

BCEH Bureau of Community & Environmental Health.

Carcinogen A substance that causes cancer.

Chronic Occurring over a long time (more than 1 year).

Comparison value (CV) Calculated concentration of a substance in air, water, food, or soil that is unlikely to cause harmful (adverse) health effects in exposed people. The CV is used as a screening level during the public health assessment process. Substances found in amounts greater than their CVs might be selected for further evaluation in the public health assessment process.

Confined animal feeding operation (CAFO) An enclosed area (covered or open) where animals are fed and given veterinary drugs to increase body weight before slaughter. Liquid and solid waste from CAFOs is often kept on site in lagoons or allowed to drain into surrounding areas. The term ‘feed lot’ is also used to describe an open-air CAFO.

Contaminant A substance that is either present in an environment where it does not belong or is present at levels that might cause harmful (adverse) health effects.

Drinking Water Equivalent Level (DWEL) Intermediate drinking water quality parameter, derived from the RfD. The DWEL is multiplied by a percentage of the total daily exposure contributed by drinking water (often 20 percent) to determine the MCLG.

Dose The amount of a substance to which a person is exposed over some time period. Dose is a measurement of exposure. Dose is often expressed as milligram (amount) per kilogram (a measure of body weight) per day (a measure of time) when people eat or drink contaminated water, food, or soil. In general, the greater the dose, the greater the likelihood of an effect. An "exposure dose" is how much of a substance is encountered in the environment. An "absorbed dose" is the amount of a substance that actually got into the body through the eyes, skin, stomach, intestines, or lungs.

EPA The U.S. Environmental Protection Agency.

Exposure Contact with a substance by swallowing, breathing, or touching the skin or eyes. Exposure may be short-term [**acute**], of intermediate duration [**intermediate**], or long-term [**chronic**].

FDA The U.S. Food and Drug Administration.

Feed lot An open-air CAFO.

Groundwater Water beneath the earth's surface in the spaces between soil particles and between rock surfaces.

Hazardous substance Any material that poses a threat to public health and/or the environment. Typical hazardous substances are materials that are toxic, corrosive, ignitable, explosive, or chemically reactive.

Health Advisory (HA) Health Advisories (HA's) provide information on contaminants that do not have an MCL but that can cause human health effects and are known or anticipated to occur in drinking water.

Hormone A chemical that is produced by the body (endogenous) or introduced as a medication into the body (exogenous) that regulates sexual development, growth and metabolism. Hormones can be natural or synthetic (human-made). Livestock are given hormones to increase weight gain before slaughter.

IDEQ The Idaho Department of Environmental Quality.

IDHW The Idaho Department of Health & Welfare.

Indeterminate public health hazard The category used in ATSDR's health consultation documents when a professional judgment about the level of health hazard cannot be made because information critical to such a decision is lacking.

Ingestion rate The amount of an environmental medium which could be ingested typically on a daily basis. Units for ingestion rate are usually liter/day for water, and mg/day for soil.

ISDA The Idaho State Department of Agriculture, which is responsible for regulating CAFOs.

Lowest Observed Effect Level (LOEL) The lowest tested dose of a substance that has been reported to cause measurable health effects in people or animals.

Maximum Contaminant Level (MCL) Enforceable drinking water quality standard set by US Environmental Protection Agency (EPA).

Maximum Contaminant Level Goal (MCLG) Non-enforceable drinking water quality standard, used to determine the MCL.

Media Soil, water, air, plants, animals, or any other part of the environment that can contain contaminants.

Monitoring wells Special wells drilled at locations on or off a hazardous waste site so groundwater can be sampled at selected depths and studied to determine the movement of groundwater and the amount, distribution, and type of contaminant.

Nitrate A colorless and water soluble compound containing nitrogen and oxygen. Nitrates are widely used in human food supplies as curing agents and preservatives. Nitrates enter drinking water from fertilizer runoff, sewage, and natural erosion of soil and rock.

No apparent public health hazard
A category used in ATSDR's health consultation reports for sites where human exposure to contaminated media might be occurring, might have occurred in the past, or might occur in the future, but where the exposure is not expected to cause any harmful health effects.

No Observed Effect Level (NOEL)
The highest tested dose of a substance that has been reported to have no measurable health effects on people or animals.

No public health hazard
A category used in ATSDR's public health assessment documents for sites where people have never and will never come into contact with harmful amounts of site-related substances.

Oral Reference Dose (RfD) An amount of chemical ingested into the body (i.e., dose) below which health effects are not expected. RfDs are published by EPA.

Organic Compounds composed of carbon, including materials such as solvents, oils, and pesticides which are not easily dissolved in water.

Pesticide Any agent designed to kill pest organisms. Herbicides are pesticides designed to kill weeds. Insecticides are pesticides designed to kill insects.

Plume A volume of a substance that moves from its source to places farther away from the source. Plumes can be described by the volume of air or water they occupy and the direction they move. For example, a plume can be a column of smoke from a chimney or a substance moving with groundwater.

Public Health Hazard A category used in ATSDR's health consultation reports for sites that pose a public health hazard because of long-term exposures (greater than

1 year) to sufficiently high levels of hazardous substances that could result in harmful health effects.

Route of exposure The way people come into contact with a hazardous substance. Three routes of exposure are

breathing [inhalation], eating or drinking [ingestion], or contact with the skin [dermal contact].

Safety factor A number that is used to account for uncertainty in the data and/or severity of the health effect when calculating an oral RfD or other level or dose to which humans can safely be exposed. Safety factors generally range from 1-100.

Steroid Hormone A group of hormones that are derived from cholesterol and are fat-soluble.

WHO The World Health Organization.